

## Precision Medicine: Is Malaysia ready?

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### REVIEW ARTICLE

Precision medicine is mainly about genome-driven clinical decision-making which is the use of genome data from the patient to decide on tailoring the best treatment for the patient. The completion of the human genome project in 2003 has paved the way for a deeper understanding of diseases at the molecular level. The term genomics medicine has since emerged as clinicians and researchers capitalized on the knowledge of the genome to improve the management of many diseases. In the past decade, the term personalized or precision medicine was introduced to represent the tailoring of treatment to each individual based on a person's unique genetic makeup, environment and lifestyle [1]. The coining of the term precision medicine, as opposed to the more common term 'personalised medicine', was intended to highlight the principle that subgroups of patients could be defined, often by genomics, and given treatment in more specific ways [2]. In simple terms, it means giving the right treatment to the right patient at the right time with the right outcome. The concept is not entirely new as it has been applied before in the practice of blood transfusion where each patient is given the appropriate blood units based on their blood groups. However, the emergence of genome data has allowed a more comprehensive application of personalized medicine to make it more precise. The unravelling of the molecular events in certain diseases like cancers has also led to the development of targeted therapies.

For a long time, doctors have been treating patients with the same disease using the same approach, the same drugs and the same dose. The outcomes of treatment have strongly suggested that the individual variation, especially the genetic variants which differ between individuals, must be taken into account and the one-size fits all approach is no more valid for many diseases. Studies have shown that anti-cancer drugs are effective in perhaps 25% of cases only, that 6-8% of patients given medications will have adverse reactions, that there is a wide variation in response to

treatment from one patient to another despite giving the same dose (adjusted per kg body weight) of the same drug, and that many non-communicable diseases have the component of gene-environment interaction in terms of disease pathogenesis. It is time for clinicians to tailor the treatment individually not only based on the phenotype but also on the genotype of the disease, provided there is evidence to show the benefit of a personalized approach [3].

The advances in genome sequencing technologies, and the cheaper cost, has allowed more and more patients to be profiled at the molecular level. There are still a lot to be learned but certainly we know more than before. In the case of cancers, the whole genome sequencing of tumour tissues has enable us to understand that every tumour has its own molecular signature which has both prognostic value but also has allowed researchers to identify what is termed now as actionable or targetable mutations. The term 'targeted therapy', once labeled decades ago as the magic bullet for the treatment of cancer, is now a reality for many different types of cancer. Many tyrosine kinase inhibitors are now in the market and used to improve the outcome of cancer patients.

Many developed nations have already launched big initiatives in precision medicine in the past 5 years. In 2012, the Prime Minister of UK launched the 100,000 Genomes project in England. The project aim was to sequence 100,000 genomes which will include cancers, rare diseases and also pathogens [4]. The project is spearheaded by the National Health Service (NHS) with extensive collaboration with top university hospitals and the industry. One of the earliest benefactor of the project was a young girl with a rare disorder. She presented with a history of seizures and despite many tests and investigations, the doctors failed to clinch a diagnosis. Whole genome sequencing was performed on her and both parents. The bioinformatics analysis on the sequence data revealed a deletion in one copy of her SLC2A1 gene.

This gene plays a role in the uptake of glucose into the brain cells. She was put on a ketogenic diet and her seizures have stopped. Another wonderful example is the case of 3 sisters who all developed breast cancers within a few years of each other. What was interesting is that they did not inherit the BRCA1 or BRCA2 mutation. These were just two of the many examples how whole genome or whole exome sequencing has enabled the diagnosis of many rare diseases and cancers, and in a proportion of the patients, to identify the specific intervention as well. It is believed that the approach of precision medicine can solve between 30-40% of rare diseases.

In the USA, President Obama launched a precision medicine initiative (PMI) in 2015 with a USD215 million grant, focusing on non-communicable diseases, including cancers, and also setting up of a Cohort project [5]. This initiative, similar to the UK 100,000 genomes project, will also performed whole genome sequencing on selected diseases. This project was triggered by the meeting of a group of scientists, which included Dr. Francis Collins, the then director of the National Institutes of Health USA, with the president. The other central feature of the USA PMI is the establishment of a new 1-million-person cohort of individuals who are willing to contribute their data for scientific discovery.

The precision medicine initiatives in both the UK and the USA, reflected how the political will as a key driver in making things happen. But in both cases too, the prime movers were the scientists and the doctors who share the same belief and vision as to how genomics and precision medicine will be able to change the way we treat patients. In the simple sense, this is the future of medicine.

How is Malaysia responding to all these? There has been very little movement or response at the top level. We need a lot more resources if we were to adapt this precision medicine in big way. There are clear challenges here. Firstly, the cost of the genetic testing or genotyping of the diseases. This is not covered under our healthcare system and many of these tests will cost easily between RM2000-5000. Some laboratories are absorbing some of these tests under their research grants but this is truly not sustainable once the funds run out of money. What needs to be done is that if, and when, the health financing system is implemented in Malaysia, we hope that genetic testing will be covered by the insurance companies. The second challenge is that if the genetic testing identifies a targetable mutation, there will additional cost of the tyrosine kinase inhibitors or the precision treatment. Again at the moment, many of these drugs are not in the 'blue' book or the list of drugs which are

given free hence this will be the out-of-pocket expenses for the patient which can run into thousands of ringgit. The third challenge is how genetic testing will impact on the eligibility for medical insurance coverage. In some countries, there is a law prohibiting the use of genetic data to deprive an individual from getting medical insurance coverage but in Malaysia there is none yet. This means that if someone tested positive for the BRCA1 gene, for susceptibility to the familiar breast cancer, then the individual will not be able to obtain medical insurance coverage.

The 3 challenges mentioned in the previous paragraph are not insurmountable if someone takes the leadership to tackle them at the top level. If Malaysia wants to be an early adapter to precision medicine, we truly need someone to champion this and most importantly the political will, just like in the UK and the USA.

At the UKM Medical Molecular Biology Institute (UMBI), Universiti Kebangsaan Malaysia, we have already started offering tests for precision medicine. We have recently performed whole exome sequencing on patients with Pendred syndrome and VACTERL-H syndrome and discovered disease-causing mutations in the cases [6]. Our institute is arguably the first in the country to offer whole exome or whole genome sequencing for rare diseases. UMBI is already offering pharmacogenetics testing for HLA-B\*1502 [7]. UMBI is also already offering whole genome and whole exome sequencing services to a wide variety of patients including cancers and rare diseases. Our institute has also embarked on whole genome sequencing of colorectal cancers which is funded by a research grant from the Ministry of Higher Education. This project is the first and largest of its kind in the local setting.

Let's now have a peek at the scope of precision or personalized medicine and the various applications which will directly benefit the patients (Table 1).

What are the resources needed to implement precision medicine? We certainly need good sequencing facilities which must also have skillful and knowledgeable geneticists, scientists and bioinformaticians. The bioinformaticians will develop to adapt the optimal analytical algorithms to suit the clinical needs. For precision medicine to be successful, it needs to be accurate as well hence the understanding of the genetic variation at the population level needs to be wide and deep. This is even more crucial in a country like Malaysia which has a large multi-ethnic population.

The personalized and precision medicine approach is already driven by the genome sequencing technologies

**Table 1. The scope of precision medicine and how it is applied.**

Scope	Application
Risk assessment	Genetic testing will be able to reveal one's predisposition to disease. One example is the BRCA1/2 gene testing which will identify those at high risk of developing breast cancer. Others include the APC gene which is the gene responsible for the familial adenomatous polyposis that in turn increases the risk of colon cancer.
Diagnosis and classification	Genetic testing will allow accurate diagnosis allowing individualized treatment strategy. For rare diseases and also diseases which are difficult to diagnose, the precision medicine approach will enable a diagnosis to be clinched in up to 40% of cases. For disease classification, a good example will be in primitive neuroectodermal tumours (PNET) which are common brain tumours in children. There is now a molecular classification of PNET which takes into account alteration in the FOXR2, CIC, MN1 and BCOR genes [8].
Prevention	Genetic testing will also allow behaviour/lifestyle/treatment intervention to prevent disease. A good example is the detection of genetic variants or polymorphisms which confer a high risk of non-communicable diseases such as diabetes. Another example is the detection of Lynch syndrome which involves the testing of MLH1, MSH2, MSH6 and PMS2 genes [9]. Those who have mutations in these genes will have a 70% lifetime risk of getting colorectal cancer.
Detection	Many cancers release nucleic acids and other biomarkers into the circulation. Detection of molecular markers circulating in the blood (liquid biopsy) will enable the early detection of cancer or also disease relapse.
Treatment	The most impactful example for precision medicine is in cancer treatment. Genomic characterization has in fact been standard of care for some time for lung adenocarcinoma: testing for specific epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma receptor tyrosine kinase (ALK) rearrangements allows the personalization of therapy with targeted kinase inhibitors, such as gefitinib for EGFR and crizotinib for ALK23,24 [10]. For cancer, one can do whole exome or whole genome sequencing to identify the actionable or targetable mutations [11]. Another option is to use customized cancer panels which covers a certain of number genes containing the candidate mutations. In cardiology, for patients with the Long QT syndrome, there is specific therapy for those who have SCN5A mutations. Another big application is in pharmacogenetics which is perhaps the first application of personalized medicine. A good example in practice now is the testing for HLA-B*1502 polymorphism before commencing tegretol for patients with epilepsy. Patients who have this genetic variant will have a high risk of developing Stevens Johnson syndrome.
Prognostication	Certain molecular profiles confer a poorer prognosis in certain diseases. For example, in paediatric patients with medulloblastoma, those in the WNT sub-group have an excellent outcome [12]. Serial fluid biopsies and molecular testing can help the active monitoring of disease response and disease progression. There are also gene expression panels to predict prognosis for colorectal cancer [13].

and also Big Data. As we accrue more sequencing data from patients, we will learn more about the diseases and potentially this can lead to better approaches to management. Whether Malaysia is ready or not, precision medicine is already here for us to utilize and leverage on for the benefit of our patients. At this moment, it is very much for those who are subsidized

or those who can afford to pay for the genetic testing and the cost of the subsequent targeted therapies. There is certainly a need to do cost-effectiveness and cost-benefit analysis and present the information to the relevant authorities and to convince them that precision medicine is the way forward.

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